UNIVERSITI TEKNOLOGI MARA

AN APPROACH TOWARDS THE SYNTHESIS OF DYSIDAMIDE C AND ITS DERIVATIVES

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the result of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any other degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of mu study and research.

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ABSTRACT

Dysidamide C was chosen in this study as the synthetic target due to its unique skeletal structure and its interesting pharmacological activities. This thesis has been divided into five main sections. Chapter one is a review on our target compounds-Dysidamide C. Chapter two focus on the synthetic strategies of compound which have similar skeleton to Dysidamide C by different research groups, whilst chapter three consists of our synthetic works. Experimental details including the spectroscopic data are provided in chapter four and finally, future works are recommended in chapter five. Our synthetic approach towards the synthesis of Dysidamide C was divided into two different routes. The first route began by couple up readily available starting material known as glycine methyl ester and methyl malonate potassium through condensation reaction followed by Dieckmann cyclisation to give pyrolidine ring known as the β,β-diketoester. Letting β,β-diketoester undergo a series of successive chemical reactions, which include demethoxycarbonylation, dialkylation at C-3 position, olefin formation at C-5, successfully gave our desire template known as methylene ketone type of compounds, **125** (with an overall yield of 21%). For the second route, methylene ketone type of compounds, **125**, was obtained in four steps using methyl acetoacetate as the starting material. The first step was known as dimethylation, followed by brominations, intercyclization reaction and finally olefin formations at C-5 (with an overall yield of 26%). This entire attempt was successfully furnished us with over 35 pyrrolidine type of compounds. Apart from that, we manage to manipulate the important intermediates **125**, to produce Dysidamide C-derivative known as diesterified compound and *iso*xazoline in 4 steps. In brief, we have developed a mild and operationally simple procedure towards the synthesis of Dysidamide C. The result extracted from this study thus far may be used to develop new scientific knowledge and remarkable findings.

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CHAPTER ONE

INTRODUCTION

1.1 MARINE NATURAL PRODUCT AS A POTENTIAL SOURCE FOR DRUG DISCOVERY

Nature continues to be one of the most important sources of pharmacologically active compounds in the quest for drugs against life threatening diseases. Traditionally, plants have been in the focus for the search of new drug candidates from nature. However, in recent years, the new trend in drug discovery from nature is emphasized more on marine organism such as sponge, tunicate, coral and algae, due to their unique existence of secondary metabolites and their pharmacologically active properties [1-2]. Six hypotheses have been summarized by Haslam *et. Al.* [3] which were supported by Williams [4] and Harbone [5] on the origin of the secondary metabolites from non-proteinaceous natural products that has long intrigued chemists and biochemists. According to Haslam, secondary metabolites are simply waste products with no particular physiological role. Secondly, secondary metabolites are products that at one time had a functional metabolites role, which are now lost. Thirdly, secondary metabolites are compounds of random mutation and have no real function in organism. Fourthly, secondary metabolites are an example of an evaluation in progress and provide pool of compounds out of which new biochemical processes can emerge. Apart from that, secondary metabolites provide ways of enabling the enzyme of primary metabolism to function when there are not needed for their primary purpose and finally, secondary metabolites play a key role in organism's survival and other physiologically important compounds. This hypothesis is consistent with the fact that in nature, these secondary metabolites serve as chemical defense that protect these soft bodies, shell-less invertebrates from intense competitions and harsh condition in marine environment [5-6].